CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210115Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Renata Albrecht, MD Ozlem Belen, MD, MPH
Subject	Division Director Summary Review Deputy Director for Safety & CDTL Review
NDA	NDA 210115
Related IND	IND 64148
Applicant	Astellas Pharma, Inc.
Date of Submission	July 26, 2017
PDUFA Goal Date	May 26, 2018 (Saturday)
Proprietary Name	PROGRAF® Granules
Established or Proper Name	tacrolimus for oral suspension
Dosage Form(s)	Packets (b) (4) containing granule that are to be reconstituted with water to make an oral solution before administration to the patient
Applicant Proposed Indication(s)/Population(s)	Prevention of rejection in pediatric liver, kidney and heart transplant patients
Action or Recommended Action:	*Approval*
Approved/Recommended Indication(s)/Population(s) (if applicable)	*Prevention of rejection in liver, kidney and heart transplant patients*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Ergun Velidedeoglu, Ozlem Belen, Renata Albrecht, 05/23/2018
Statistical Review	Hongling Zhou, Yan Wang, 05/15/2018
Pharmacology Toxicology Review	Aaron Ruhland, Lori Kotch, 04/13/2018
OPQ Review	See table below
Immunology/Microbiology Review	Shukal Bala, 01/09/2018
Clinical Pharmacology Review	Abhay Joshi, Phil Colangelo 05/22/2018
OPDP	Carrie Newcomber 04/25/2018
OSIS	Mohsen Abhari, Arindam Dasgupta, Charles Bonapace, 03/26/2018
CDTL Review	Ozlem Belen, 04/18/2018, 05/08/2018
OSE/DMEPA	Madhuri Patel, Sarah Vee, 04/19/2018, 05/22/2018 Azeem Chaudhry, 05/09/2018
Proprietary Name Review and Granted Letter	Madhuri Patel, Sarah Vee, Mishale Mistry 05/18/2018 Danielle Harris 05/21/2018
OSE/DMPP	Karen Dowdy, Carrie Newcomer, Sharon Williams, LaShawn Griffiths 05/02/2018
OND/DPMH	Yeruk (Lily) Muludeta, Hari Sachs 05/18/2018
Project Manager	Wendy Streight, CPMS Diana Willard

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality,
OPDP=Office of Prescription Drug Promotion
OSIS=Office of Study Integrity and Surveillance
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Programs
DPMH-Division of Pediatric and Maternal Health

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Application Technical Lead	Chunchun Zhang	NA
Drug Substance	Sharon Kelly	Charles Jewell
Drug Product	Yushi Feng	Bala Shanmugam
Microbiology	Nancy Waites	Dan Obrzut
Biopharmaceutics	Joan Zhao	Jing Li
Process	Nancy Waites	Dan Obrzut
Facility	Ebern Dobbin	Derek Smith
Regulatory Business Process Manager	Kristine Leahy	NA
ORA Lead	Caryn McNabb	NA
Laboratory (OTR)	NA	NA
Environmental Assessment (EA)	Yushi Feng	Balajee Shanmugam

Source: Quality Assessment Review #1 April 10, 2018

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment
PROGRAF® Granules (tacrolimus for oral suspension) is a new formulation of tacrolimus developed by Astellas, and submitted in response to a Post-Marketing Requirement (PMR) for ASTAGRAF XL (NDA 204096, Astellas) in response to the requirement to develop a pediatric formulation to be used in pediatric patients 1 to < 5 years of age. The product comes as granules in single-dose packets which are then reconstituted with water to an oral suspension before being administered to the patient. The labeling includes Patient Information and Instructions for Use, two documents that are intended to be provided to the patient (or patient care giver) so they are familiar with information about Prograf and how to prepare the oral solution. The currently approved calcineurin inhibitors (CNI) are tacrolimus and cyclosporine. Tacrolimus is the CNI immunosuppressant used by the majority of transplant patients based on the reports from the Systematic Registry of Transplant Recipients (SRTR). Tacrolimus is currently available in oral capsules or injection form. The availability of a formulation for oral suspension means patients will not need to obtain product from compounding pharmacies to administer tacrolimus to an infant, toddler or younger child who cannot swallow capsules. Cyclosporine, the other CNI approved for prophylaxis of organ rejection is not used as commonly in transplantation as it was in the last century, although it is available in oral solution. The applicant submitted results of a prospective, adequate and well controlled pediatric liver transplant study that supports the efficacy and safety of tacrolimus when it was compared to a regimen with cyclosporine. The labeling has been updated to include the starting dose and target trough levels for pediatric patients receiving liver transplants, and the adverse reactions and efficacy information has been included in the Adverse Reactions and Clinical Studies sections of labeling, respectively, showing that the tacrolimus based regimen had a favorable safety profile and resulted in fewer acute rejections, deaths and graft loses compared to a cyclosporine based maintenance immunosuppressive regimen. Although no randomized controlled trials have been performed and submitted to the application in pediatric heart or kidney transplant recipients with the granule formulation, tacrolimus is commonly used in pediatric (heart or kidney) transplant patients. Based on discussions with the Pediatric Review Committee, use of PROGRAF capsules and PROGRAF Granules (tacrolimus for oral suspension) in pediatric kidney and heart transplant patients is supported by adequate and well controlled studies in adult kidney and heart transplant patients with additional pharmacokinetic data from adult and pediatric patients and safety data in pediatric liver transplant patients. Working with PeRC, the Applicant and the review team, the Dosage and Administration Section (2.4) has been updated to provide recommended initial oral dosing for all three pediatric indications.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Organ transplantation is the preferred management of end-stage kidney, heart and liver disease, preferable to dialysis • Patient who receive allogeneic organs need life-long immunosuppression to prevent their immune system from rejecting the organ	Organ transplant recipients need life-long immunosuppression to prevent organ rejection
Current Treatment Options	• There are multiple drug classes available for immunosuppression as provided in the Medical Officer Review, however the most commonly used include induction, and maintenance regimen of tacrolimus, mycophenolate and steroids.	This application provides for a pediatric formulation (tacrolimus for oral suspension) that can be taken by patients who cannot swallow capsules, generally those <5 years of age.
Benefit	• Tacrolimus has been shown to be an effective immunosuppressant (IS) in preventing rejection in kidney, heart and liver transplant patients • IS are used in combination to be effective • This formulation can be used in patients who cannot swallow tablets	This product addresses an unmet need in pediatric patients who are otherwise given compounded products. Medication errors with compounded products has been reported to FDA (OSE Review).
Risk and Risk Management	• Adverse reactions associated with tacrolimus are well known and no new ones have been identified in pediatric patients. • Risks are managed by careful dosing, maintaining target trough tacrolimus levels using therapeutic drug monitoring, and adjusting doses and trough levels to maximize benefit (prevention of rejection and graft loss) and minimizing the risk (managing any treatment related adverse events • There is the potential risk of not preparing the product correctly; that risk is likely to be managed by the transplant staff when a pediatric patient receives an organ transplant and the parents or health care providers are trained on how to determine the correct number of packets based on the dose, how to prepare the packets containing granules used to make the oral solution, and what resources are available (labeling, healthcare provider, etc.) when questions or concerns arise.	Immunosuppression is a life-long therapy, which must be managed by experts in the field. Tacrolimus and other products are managed by TDM, and benefits are maximized, risks minimized to the extent possible for the patient. This oral solution formulation can be used by patients who cannot swallow tacrolimus capsules.

2. Background

PROGRAF® Granules (tacrolimus for oral suspension, NDA 210115) was submitted by Astellas in response to a Post-Marketing Requirement (PMR), namely PMR 2601 – 1 in the approval letter for ASTAGRAF XL (tacrolimus-extended release capsules, NDA 204096, Astellas) to address the requirement to develop a pediatric formulation to be used in pediatric patients 1 to < 5 years of age.

PROGRAF® capsules in strengths of 0.5, 1 and 5 mg (NDA 50708) and PROGRAF® injection (NDA 50709) were formulations approved for liver transplant in 1994, for kidney transplant in 1997 and heart transplantation in 2006. Generic forms of tacrolimus capsules are currently marketed.

Tacrolimus for oral suspension was first approved in Japan in 2001 as Prograf Granules, and was approved in Europe in 2009 as Modigraf ®. It is currently marketed in 32 countries.

Pre-NDA meeting was held 10-17-2016 (minutes dated 11-16-2016) to discuss content, format, and studies to be submitted to support the application.

3. Product Quality

The following summary is based on the CMC review of the application; the full review provides more detailed information. CMC recommends approval of the application:

The product comes as granules in single-dose packets, manufactured in strengths of 0.2 mg and 1 mg. The granules are reconstituted with water to an oral suspension before being administered to the patient. The drug substance is tacrolimus, a white crystals or crystalline powder. It is manufactured by Astellas Pharma Inc. All excipients are qualified and no novel ones are used in the formulation.

Name of Ingredients	Tacrolimus Granules 0.2 mg [mg/packet] [3]	Tacrolimus Granules 1 mg [mg/packet]	Rationale	Reference to Quality Standard
Tacrolimus [1]	0.2	1.0	Active ingredient	USP, US DMF#16833
Hypromellose	(b) (4)			USP
Croscarmellose Sodium				NF
Lactose Monohydrate				NF
Total				-
(b) (4)				

The manufacturing process of the tacrolimus granules differs from the already licensed product (b) (4) (b) (4). This difference is because the currently licensed product is filled into capsules (b) (4).

The drug product specification includes tests for appearance, identity, assay, impurities, dissolution, content uniformity, and microbial limits. The proposed specification is acceptable to ensure quality of the product over its expiration period. All analytical methods are described in reasonable detail and have been adequately validated.

The biopharmaceutics review has found the proposed dissolution method and acceptance criterion (NLT (b) (4)% (Q) in 45 minutes) acceptable. The formulation of the commercial tacrolimus for oral suspension is the same as the clinical batches, except for the manufacturing site and scale. The bridge between the clinical batches and the commercial product is supported by the comparative dissolution profile.

Batch analyses are provided for 6 batches for each strength on commercial scales (b) (4) (b) (4) which were manufactured by Astellas Pharma Inc. All batches complied with the proposed specification.

Drug product stability data are available to 36 months at long term storage 25°C/60%RH and 6 months at accelerated conditions 40°C/75%RH for two strengths with 6 registration batches. There is no trend observed for all tests when the drug products were stored at long term or accelerated condition. The shelf life of 36 months when stored at 20°C-25°C is granted.

(b) (4)

The storage statement is “Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

The container-closure systems for both strengths are the same, a packet. The packet is composed of aluminum foil (b) (4) (b) (4).

The NDA, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product tacrolimus for oral suspension. All information requests and review issues have been addressed. The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 4/6/2018. NDA 210115 is recommended for approval from Product Quality perspective

4. Nonclinical Pharmacology/Toxicology

The following is a summary from the Pharmacology/Toxicology Review, which contains more detail, Pharmacology Toxicology recommends approval of the application:

The studies relied on for this 505(b)(1) application were previously reviewed under NDA 50708, and no new studies are submitted. Within this application, Section 8 of the labeling is being converted to conform with the Pregnancy and Lactation Labeling Rule (PLLR) format.

No new nonclinical findings were reported or discovered during review of this application, however several nonclinical findings that were included in earlier reviews of NDA 50708 were not included in the current version of the labeling; these are included in labeling during this review cycle. All changes in the labeling to conform with PLLR format are derived from studies previously reviewed for approval of other formulation of tacrolimus. Revisions to Sections 8.1, 8.2, 8.3 and Section 13 are reflected in the attached Prescribing Information.

5. Clinical Pharmacology

NDA 210,115 is supported by two clinical efficacy and safety studies, FG-506-01-08 and FG-506-01-13; two pharmacokinetic studies, F506-CL-0403 (OPTION) and F506-CL-0404A (PROGRESSION); and a healthy subject bioequivalence study 95-0-001. Clinical Pharmacology recommends approval of the application.

The following is a summary from the Clinical Pharmacology Review, which contains more detail.

- The pivotal evidence of effectiveness for PROGRAF granules in the pediatric liver transplant prophylaxis indication is derived from Study FG-506-01-13 (Phase 3) and supported by Study FG-506-01-08 (Phase 2).

- The pharmacokinetic evidence for support of pediatric heart, kidney, and liver transplantation is derived from the following three studies:
  - Study F506-CL-0403 (OPTION) (Phase 4)
  - Study F506-CL-0404A (a follow-up study to the OPTION study)
  - Study 95-0-001 (Phase 1)

- The Applicant's proposed starting oral dose of PROGRAF granules for pediatric liver transplant patients was the same as the currently approved dose for PROGRAF capsules, i.e., 0.15 - 0.20 mg/kg/day to be administered in two divided doses, every 12 hours. However, the starting dose evaluated in the pivotal Phase 2 and Phase 3 studies listed above was approximately 0.3 mg/kg/day.
  Based on the information in original submission and the Applicant's response to an IR, the Clinical Pharmacology review team recommends that the starting dosing for tacrolimus granules for pediatric liver transplantation be changed in the USPI to *0.20 mg/kg/day to be administered in two divided doses, every 12 hours*.

- Pharmacokinetic findings from a single dose healthy volunteer adult study indicated that the systemic exposure (AUC) to tacrolimus from PROGRAF granules was approximately 16% higher than that from PROGRAF capsules. The mean Cmax for PROGRAF granules was approximately 23% higher than PROGRAF capsules. This difference is not considered clinically significant. The Applicant is proposing (b) (4) dosing conversion between formulations along with therapeutic drug monitoring following a conversion to ensure that systemic exposure to tacrolimus is maintained.

6. Clinical Microbiology

Not applicable – this product is not being developed as an anti-infective

7. Clinical/Statistical-Efficacy

The following is a summary based on the Clinical and Statistical Reviews of this application, the Reviews provide more detail. Clinical and Statistical disciplines recommend approval of the application.

NDA 210115 is supported by the following clinical studies:

- Study FG-506-01-13 is a randomized controlled study conducted with tacrolimus for oral suspension, where patients were randomized to tacrolimus and steroids versus cyclosporine-modified emulsion, azathioprine and steroids, and evaluated for efficacy (acute rejection, graft loss, death) as well as safety (adverse reactions reported during the study were collected and analyzed. The findings from this study are reflected in the Prescribing Information, Sections 14.4 and 6, respectively.
- Study FG-506-01-08 are single arm, noncomparative study and provides supportive clinical data.
- Since tacrolimus is a known molecular entity, marketed since 1994, one adequate and well controlled study is considered sufficient to demonstrate the efficacy and safety of this new formulation, tacrolimus for oral suspension.

Study 13 was a randomized study in primary pediatric liver allograft transplant patients that compared tacrolimus granules and low-dose corticosteroids with cyclosporine-microemulsion, low-dose corticosteroids and azathioprine. The study was designed as a superiority study, conducted in Europe and completed in 2000. The patients enrolled in this study ranged in age from 0.3 to 16 years of age, average age of 3.5 years. The primary endpoint was the incidence and time to first acute rejection (AR) at 12 months. The statistical review examined primarily efficacy results of the "composite endpoint" of BPAR/GL/D/LTFU (biopsy proven acute rejection/graft loss/death/LTFU)

In Study FG-506-01-13, the starting dose of tacrolimus granules in de novo liver transplant recipients was 0.3 mg/kg per day administered in 2 divided doses. However, in the proposed PI, the recommended starting dose of tacrolimus capsules is 0.15-0.20 mg/kg/day. In response to a rationale for this difference, the Applicant noted that after the starting dose, subsequent doses were adjusted based on target whole blood trough levels (10 to 20 ng/mL in the first 2 weeks; 10 to 15 ng/mL during weeks 3 and 4; 5 to 15 ng/mL during months 2 and 3; 5 to 10 ng/mL thereafter). The median initial dose of 0.29 mg/kg per day resulted in median trough levels that were on the high end of the target range for at least 50% of patients ($P50 \geq 18.2$ ng/mL) and above the range for at least 40% of patient ($P60 \geq 20.8$ ng/mL) during the first 2 days posttransplant (days 0 and 1). By days 2 and 3 posttransplant, the median dose was adjusted down to 0.17 and 0.14 mg/kg per day, respectively, resulting in median trough levels of 16.8 ng/mL and 14.4 ng/mL on days 3 and 4. For the rest of the trial, trough values were maintained within the target ranges for most patients via therapeutic drug monitoring (TDM).

Results

Patient disposition in this study included discontinuation, primarily due to adverse reactions. Based on review of the application, it was noted that acute rejections were listed as ADRs. These events were reported more frequently in the control arm of the study.

Patient Disposition (ITT population)

	Tacrolimus Granules			Cyclosporine		
	Total N=91	<5 Y N=70	≥5 Y N=21	Total N=90	<5 Y N=70	≥5 Y N=20
Completed	**68 (74.7)**	**53(75.7)**	**15(71.4)**	**44 (48.9)**	**32(45.7)**	**12(60)**
Discontinued	**23 (25.3)**	**17(24.3)**	**6(28.6)**	**46 (51.1)**	**38(54.3)**	**8(40)**
study	11 (12.1)	7(10)	4(19.0)	35 (38.9)	31(44.3)	4(20)
treatment	3(3.3)	3(4.3)	0	3(3.3)	2(2.9)	1(5)
Adverse Event	4 (4.4)	2(2.9)	2(9.5)	1 (1.1)	0	1(5)
Retransplant	3(3.3)	3(4.3)	0	3(3.3)	2(2.9)	1(5)
Protocol prohibited	2 (2.2) 0	2(2.9) 0	0 0	3 (3.3) 1 (1.1)	3(4.3) 0	0 1(5)

Source: Statistical Review (citing Table 12.1.1.3.1 of the Clinical Study Report and reviewer analysis)

Patient demographics show there is a reasonable balance in most parameters including gender, race, weight, donor type and ABO matching.

Patient Demographics:

	Tacrolimus Granules			Cyclosporine- ME		
	Total N=91	<5 years N=70	≥5 years N=21	Total N=90	<5 years N=70	≥5 years N=20
Age						
Mean(s.d.)	3.5 (3.9)	1.6 (1.2)	9.9 (3.2)	3.5 (4.2)	1.5 (1.3)	10.3(3.6)
range	0.3-15.0	0.3-4.8	5.0-15.0	0.1-16.0	0.1-4.9	5.0-16.0
Sex						
Male	46 (50.5)	35 (50)	11 (52.4)	48 (53.3)	33 (47.1)	15(75)
Female	45 (49.5)	35 (50)	10 (47.6)	42 (46.7)	37 (52.9)	5 (25)
Race						
Caucasian	75 (82.4)	59(85.5)	16(76.2)	80 (88.9)	62(88.6)	18(90)
Black	6 (6.6)	6(8.7)	0	3(3.3)	2(2.9)	0
Asian	6 (6.6)	2(2.9)	3(14.3)	4(4.4)	3(4.3)	0
Other	3 (3.3)	2(2.9)	2(9.5)	3(3.3)	3(4.3)	2(10)
Unknown	1(1.1)	1(1.4)	0	0	0	0
Weight (kg)						
Mean(s.d.)	14.6(10.3)	10.0(3.9)	29.9(10.2)	13.9 (10.7)	9.2 (3.5)	30.0(11.8)
range	5.0-51.3	5.0-23.0	14.0-51.3	3.0-60.0	3.0-21.0	14.0-60.0

Living related donor Yes No	10 (11.0) 81 (89.0)	9 (12.9) 61(87.1)	1(4.8) 20 (95.2)	11 (12.2) 79 (87.8)	11 (15.7) 59 (84.3)	0 20 (100)
ABO match Identical compatible	75 (82.4) 16 (17.6)	59(84.3) 11(15.7)	16(76.2) 5(23.8)	75 (83.3) 15 (16.7)	57 (81.4) 13 (18.6)	18 (90) 2 (10)

Source: Statistical Review {citing Table 3 of the Clinical Study Report and reviewer analysis}

Efficacy Results by Treatment Group at 12 Month are displayed below showing there is a numerically lower rate of outcome in terms of rejection and graft loss in this study, supporting the efficacy of this formulation of Prograf.

Endpoints	Tacrolimus Granules	CsA-ME	Risk Difference (95% CI) (tacrolimus granules
ITT Population			
	N=91	N=90	
AR	39* (42.9%)	49 (54.4%)	-11.6% (-26.1%, 2.9%)
BPAR	40* (44.0%)	49 (54.4%)	-10.5% (-25.0%,4.0%)
Death	6 (6.6%)	7 (7.8%)	-1.2% (-8.7%, 6.3%)
Graft loss	7 (7.7%)	13 (14.4%)	-6.8% (-15.8%, 2.3%)
Graft loss excluding death	1 (1.1%)	6 (6.7%)	-5.6% (-13.0%, 0.2%)
BPAR/GL/D	46 (50.5)	55 (61.1%)	-10.6% (-24.9%, 3.8%)
Unknown status	2 (2.2%)	0	2.2% (-2.1%, 8.3%)
BPAR/GL/D/LTFU	48 (52.7%)	55(61.1%)	-8.4% (-22.7%, 6.0%)
< 5 years of age			
	N=70	N=70	
AR	31*(44.3%)	40 (57.1%)	-12.9% (-29.3%, 3.6%)
BPAR	32* (45.7%)	40 (57.1%)	-11.4% (27.9%, 5.0%)
Death	5 (7.1%)	7 (10%)	-2.9% (-12.1%, 6.4%)
Graft loss	6(8.6%)	12(17.1%)	-8.6% (-19.6%, 2.4%)
Graft loss excluding death	1 (1.4%)	5 (7.1%)	-5.7% (-14.5%, 1.6%)
BPAR/GL/D	37 (52.9%)	45 (64.3%)	-11.4% (-27.6%, 4.8%)
Unknown status	2 (2.2%)	0	2.2% (-2.1%, 8.3%)
BPAR/GL/D/LTFU	39 (55.7%)	45 (64.3%)	-8.6% (-24.7%, 7.6%)
≥ 5 years of age			
	N=21	N=20	
AR	8 (38.1%)	9 (45%)	-6.9% (-37.0%, 23.2%)
BPAR	8 (38.1%)	9 (45%)	-6.9% (-37.0%, 23.2%)
Death	1 (4.8%)	0	4.8% (-12.4%,24.3%)
Graft loss	1 (4.8%)	1 (5%)	-0.2% (-20.6%, 19.9%)
Graft loss excluding death	0	1(5%)	-5% (-24.9%, 11.6%)
BPAR/GL/D	9 (42.9%)	10 (50%)	-7.1% (-37.6%, 23.3%)

Unknown status	0	0	0% (-16.8%, 16.2%)

Source: Statistical Review
*Patient (b) (6) had a biopsy done for determination of PTLD (not a diagnosed AR) that revealed a BPAR. The patient was marked as an event for BPAR but not AR.
Source: Reviewer Analysis

The original recommendation for a starting dose of tacrolimus granules of (b) (4) mg/kg per day in the protocol took into consideration the following points:

- Tacrolimus therapy would be administered as a dual immunosuppressive regimen without antibody induction and without azathioprine.
- Clearance of tacrolimus in pediatric liver transplant patients is approximately 2-fold higher than in adults

Given the information provided for Study 13, the practice that tacrolimus dosing is accompanied by therapeutic drug monitoring, the clinical pharmacology and clinical reviewers considered that the recommended starting dose for the Prograf Granules should be 0.2 mg/kg/day. Of note, the current clinical practice is to use tacrolimus with mycophenolate mofetil (MMF) with/without corticosteroids, thus a lower initial dose of tacrolimus can be administered without compromising efficacy. Additionally, in the USA, the use of antibody induction in conjunction with a tacrolimus-based regimen is more common. The use of antibody induction provides immunosuppressive coverage in the immediate posttransplant period, also permitting use of lower initial dose therapy for the first 4 to 5 days of treatment.

The Dosage and Administration section of the Prescribing Information has been updated to add the starting dose of tacrolimus for oral suspension in pediatric liver transplant patients, and to add starting oral doses for pediatric heart and liver transplant patients, based on information provided by the applicant after the PeRC meeting, and reviewed by the Division. Of note, these starting doses are supported by clinical studies that were conducted in Europe with tacrolimus, and are consistent with the starting oral doses included in the Modigraf® prescribing information. Target whole blood trough concentrations for each indication are also included, and, as in adults, the pediatric troughs tend to be at the higher range early after transplantation. The doses and corresponding target troughs tend to be lower after the first months-to-years after transplantation. Pediatric patients in general need higher tacrolimus doses compared to adults; the higher dose requirements may decrease as the child grows older.

Patient Population	Initial Oral Dosage (formulation)	Whole Blood Trough Concentration Range
ADULT		
Kidney Transplant		
With azathioprine	0.2 mg/kg/day capsules, divided in two doses, every 12 hours	Month 1-3: 7-20 ng/mL Month 4-12: 5-15 ng/mL
With MMF/IL-2 receptor antagonist	0.1 mg/kg/day capsules, divided in two doses, every 12 hours	Month 1-12: 4-11 ng/mL
Liver Transplant		
With corticosteroids only	0.1-0.15 mg/kg/day capsules, divided in two doses, every 12 hours	Month 1-12: 5-20 ng/mL
Heart Transplant		
With azathioprine or MMF	0.075 mg/kg/day capsules, divided in two doses, every 12 hours	Month 1-3: 10-20 ng/mL Month ≥ 4: 5-15 ng/mL
PEDIATRIC		
Kidney Transplant		
	0.3 mg/kg/day capsules or oral suspension, divided in two doses, every 12 hours	Month 1-12: 5-20 ng/mL
Liver Transplant		
	0.15-0.2 mg/kg/day capsules or 0.2 mg/kg/day oral suspension, divided in two doses, every 12 hours	Month 1-12: 5-20 ng/mL
Heart Transplant		
	0.3 mg/kg/day* capsules or oral suspension, divided in two doses, every 12 hours	Month 1-12: 5-20 ng/mL

*0.1 mg/kg/day if cell depleting induction treatment is administered.

The application also included information on patients and normal volunteers who were receiving Prograf capsules and were converted to Prograf Granules, the conversion was 1:1 (mg:mg) and the total daily dose remained the same. Patients had therapeutic drug monitoring of whole blood trough concentrations so doses could be adjusted if needed to achieve the target whole blood trough concentration.

Conclusions: The Sponsor conducted one adequate and well controlled study in liver transplantation in pediatric patients 0.3 to 16 years of age was conducted. This study FG-506-01-13 was a randomized, multi-center pediatric trial comparing the efficacy and safety of oral tacrolimus (granules) with cyclosporine. This study showed the product to be effective. Since clinical studies were not done in pediatric kidney and heart transplant patients with this product, but PK studies were completed, the issue of extrapolation and dose selection for these patients was discussed with the Pediatric Review Committee (PeRC) as part of the Assessment

of this PMR. For details of these discussions and the resulting labeling for pediatric heart and kidney are summarized in Section 10. Pediatrics.

Based on the extrapolation to pediatric patients for kidney and heart, additional information was submitted to support labeling of the starting doses and target whole blood trough concentrations, as reflected in Section 2.4 Dosage and Administration of the prescribing information.

8. Safety

The following summary is based on the Clinical Review, which contains more detail.

7.1 Safety of PROGRAF Granules

Safety of the tacrolimus for oral suspension formulation was evaluated in pediatric patients in Study FG-506-01-13, Study FG-506-01-08, Study F506-CL-0403 (OPTION), Study F506-CL-0404A (PROGRESSION); and in healthy adult subject in bioequivalence study 95-0-001.

	PROGRAF Granules (N = 91)	**Cyclosporine (N = 90)**
Body as a Whole		
Fever	46%	51%
Infection	25%	29%
Sepsis	22%	20%
CMV Infection	15%	24%
EBV Infection	26%	11%
Ascites	17%	20%
Peritonitis	12%	7%
Cardiovascular System		
Hypertension	39%	47%
Digestive System		
Liver Function Tests Abnormal	37%	28%
Diarrhea	26%	26%
Vomiting	15%	13%
Gastrointestinal Hemorrhage	11%	12%
Bile Duct Disorder	12%	8%
Gastroenteritis	12%	4%
Hemic and Lymphatic System		
Anemia	29%	19%
Metabolic and Nutritional Disorders		
Hypomagnesemia	40%	29%
Acidosis	26%	17%
Hyperkalemia	12%	10%
Respiratory System		
Pleural Effusion	22%	19%
Bronchitis	11%	8%
Urogenital System		
Kidney Function Abnormal	13%	14%

Adverse reaction information from the comparative study 13, is provided in the table below and generally shows that adverse reactions were consistent with the types of reactions reported with the oral capsule formulation. As noted under patient disposition, the discontinuation of patients from the treatment arms was lower in the Prograf arm compared to the cyclosporine control.

Information from the other studies is noncomparative, but in general includes reports of similar adverse reactions. No new adverse reactions are reported.

7.2 Pregnancy Outcome after Tacrolimus Exposure

The applicant's proposed wording for Section 8 for the Pregnancy and Lactation Labeling Rule (PLLR) conversion in this submission were reviewed by the Pharmacology/Toxicology reviewers (nonclinical studies) and Clinical reviewers (Registry and published studies of tacrolimus exposure during pregnancy). The applicant submitted a report titled "*Cumulative Analysis of Pregnancy During Use of Systemic Tacrolimus*" in Module 5.3.5.4 (Cumulative Safety Analysis – Pregnancy) of NDA 210115. Pregnancy data is also summarized in Module 2.7.4 under Summary of Clinical Safety.

The clinical review by Dr. Ergun Velidedeoglu dated May 23, 2018 and the pharmacology toxicology review by Dr. Aaron Ruhland in DARRTS dated April 13, 2018, provide more detail on the information reviewed to support the PLLR conversion.

The applicant submitted pregnancy related data from three different resources associated with tacrolimus exposure in support of PLLR labeling conversion, the Clinical reviewer performed an independent literature search:

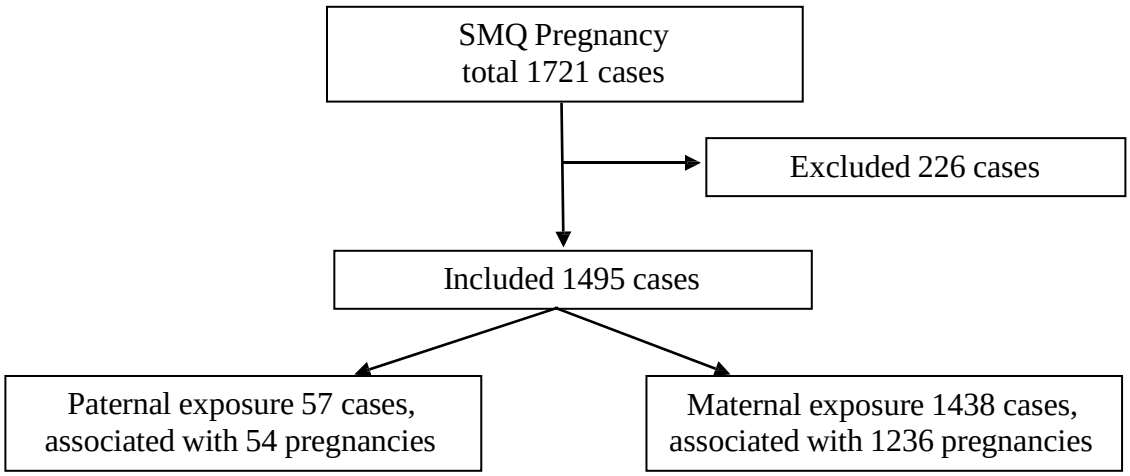
7.2.1 Astellas Argus safety database
7.2.2 Medical literature
7.2.3 Registry data
7.2.4 Clinical Reviewer's independent search of published literature

Review of the Data in Support of PLLR Conversion

7.2.1 Astellas Argus safety database:

The flowchart below shows the database search yielded 1721 cases. Of these, 226 cases were excluded: 161 cases because review revealed that there was no exposure during pregnancy; three (3) cases because they were duplicates; and a further 62 cases reported only exposure during breast feeding and not during pregnancy (these cases are considered in a separate analysis on breastfeeding and lactation). Three cases in the case series reported exposure during pregnancy as well as exposure during breast feeding, and these cases are included in the case series.

Flowchart of Pregnancy Cases



Comment: *Reasons for case exclusion were reviewed and they were appropriate.*

Of the 1495 included cases, 1438 are maternal and 57 paternal cases.

Maternal Exposures
Of the 1438 maternal exposure cases, 259 were child cases, of which 202 were linked to a maternal case that was also included in the case series. This yields a total of 1236 unique pregnancies (i.e. 1438 minus 202 to account for reports regarding the same pregnancy), including twin pregnancies and other multipara. The majority of the cases 595/1236 (43%) were related to exposure as a result of kidney or liver transplantation, overall 691 cases were associated with solid organ transplantation, others including auto-immune diseases.

Pregnancy Outcomes of 1236 Cases of Maternal Tacrolimus Exposure

Progressed to delivery (n=1066; 86%)	
Live birth	(n=1042)
No adverse event reported	576
Birth defects	89
Other events	377
Stillbirth Fetal death	24
Ectopic pregnancy (n=4; 0.3%)	4
Abortions [1] (n=166; 13%)	
Spontaneous abortion	129
Induced abortion	24
Missed abortion / incomplete / NOS	13
Total maternal exposures	**1236**

[1] **Miscarriage:** A miscarriage is the spontaneous loss of a fetus before the 20th week of pregnancy (pregnancy losses after the 20th week are called stillbirths). Miscarriage is a naturally occurring event, unlike medical or surgical abortions. A miscarriage may also be called a "spontaneous abortion." (https://medlineplus.gov/ency/article/001488 htm)
Abortion: An abortion is a procedure to end a pregnancy by medical or surgical intervention to remove the embryo or fetus and placenta from the uterus.

Birth defects after maternal exposure

A birth defect was reported in 89/1042 (8.5%) of the live birth cases in the Astellas global safety database. The birth defects/congenital anomalies included 12 reports of cardiac malformations, 9 reports of craniofacial malformations, 25 cases of multiple malformations, 20 renal/urogenital disorders, 3 skeletal abnormalities, 6 neurological abnormalities, 11 other types of birth defects, and 3 unknown/unspecified defects. Most cases had one or more risk factors such as concomitant medication (including mycophenolate mofetil) or familial disorders. However, this information was not available for all cases.

Comment: *Birth defects in maternal exposure pregnancy cases and possible confounding factors were submitted and reviewed.*

Birth defects were reported in 2/160 (1.2%) of women who received tacrolimus for indications other than prophylaxis of transplant rejection. One case was a genetic disorder (Alagille syndrome); the other had no information (PT Congenital anomaly).

Other events
In pregnant women, 17 cases of gestational diabetes and 9 cases of gestational hypertension were reported.

Prematurity
In total, 154/1042 (15%) of live birth cases in the Astellas safety database reported prematurity (PTs premature baby, premature labor, premature delivery, premature rupture of membranes, premature separation of placenta). Most of the 154 preterm cases did not report other adverse events, or only reported events typical of prematurity including low birth weight, fetal distress, or bradycardia.

Neonatal Renal Adverse Events
Neonatal renal adverse events were reported in 9/1042 (0.8%) of the live birth cases and included renal hypoplasia, renal failure, hyperkalemia and hydronephrosis among others.

Abortions
There were 24/1236 (2%) cases of induced abortion. Of these, 10 reported termination of pregnancy for medical reasons due to birth defects revealed during prenatal investigations.

Ectopic pregnancy
The 4 ectopic pregnancies occurred, all in solid organ transplant patients.

Fatal cases (including maternal deaths)
Stillbirth/fetal death was reported in 24 cases, with details provided for only some of the **c**ases. Of the maternal cases, 2 mothers died shortly after premature delivery.[2]

[2] Of the maternal cases, 2 mothers died shortly after premature delivery: One with 2 liver transplants experienced intra-renal aortic graft clotting during labor and died 2 days after delivery, more than 12 years post 2nd transplant; the second mother experienced acute and chronic liver graft rejection during pregnancy 3 years after transplant, and died 4 weeks after Cesarean-section due to cerebral aspergillus infection.

Paternal Exposures
There were 57 reported cases of paternal exposure, where the father of the child was being treated with systemic tacrolimus before or during the conception date, with a total of 54 associated pregnancies. The 3 additional cases reported involved 3 sets of twins.
Most cases (43/54, 79.6% pregnancies) were reported without adverse events. Of the 54 paternal exposure pregnancies, 51/54 (94%) progressed to delivery (all were live births) and 3/54 (6%) terminated spontaneously. Three paternal exposure cases reported a fatal outcome in the child.

Pregnancy Outcomes of 54 Cases of Paternal Tacrolimus Exposure

Progressed to delivery (n=51; 94%)		
Live birth	No events reported	43
	Birth defects	5
	Other events reported	3
Abortions (n=3; 6%)		
	Spontaneous abortion	3
Total Paternal Exposures		**54**

Five (5) out of 51 cases (10%) reported a birth defect:
- 2 cases were of genetic disorders
- 3 cases were of congenital anomaly

Three (3) paternal cases reported other events: 1 caesarean section due to twins; 1 case of meconium aspiration; and 1 premature delivery without further reported events.

7.2.2 M**edical literature:**

Pregnancy outcomes after tacrolimus exposure
A review of the medical literature was conducted by the applicant for the period up to March 31, 2016, using the key words “tacrolimus” and “pregnancy.” This resulted in 221 literature references for data analysis. The worldwide medical literature on tacrolimus identified 1607 prospectively exposed pregnancies. A moderate increase in pregnancy complications such as hypertension, pre-eclampsia, and premature delivery was observed and in the applicant’s opinion, this can be explained by the underlying disease or malfunctioning of allografts. Tacrolimus did not appear to increase the rate of congenital abnormalities.

The applicant also performed an epidemiological review of the literature in PUBMED (Limits: Meta- Analysis, Review, English, and Publication Date from 1999). In total, 61 publications were identified up to September 29, 2016. Most authors report that the use of tacrolimus at clinical doses was not associated with additional risk of congenital malformations. Generally, the results mimic the Transplant Pregnancy Registry International (TPRI) outcomes for women with renal and hepatic transplants with a live birth rate of 72-80%, a miscarriage of 14-15.6%, and a mean gestational age of 35-36 weeks. Similar to the TPRI data, the published literature suggests an increased risk of low birth weight and premature birth which may also be related to baseline condition of these patients in addition to the tacrolimus exposure.

Pregnancy outcomes in non-transplant patients
Only a small number of pregnancies (n=40) concerned non-transplant patients. Fifteen patients received tacrolimus respectively for lupus nephritis (N = 10), SLE (N = 3), ulcerative colitis or adult-onset Still's disease (N = 1 each). No pregnancy complications were reported for these non-transplant patients. All deliveries took place after 37 weeks gestation, with adequate birth weight, suggesting that many of the reported pregnancy complications after transplant may be a consequence of the transplant procedure and/or underlying disease, rather than from tacrolimus.

7.2.3 Registry data

The National Transplant Pregnancy Registry was established in 1991 to study the outcomes of pregnancies in transplant recipients in North America, but its name was changed to Transplant Pregnancy Registry International (TPRI) in 2016 and its role was extended to be an international data repository.

Pregnancy Outcomes in Organ Transplant Recipients
As of December 2015, the TPRI reported that a total of 2,609 pregnancies in 1,461 recipients and 1,359 pregnancies fathered by 879 recipients were entered the TPRI. Most pregnancies registered are in the kidney transplant group. Transplant recipients receiving immunosuppressants show the estimated risk of major birth defects was 4.3% in kidney and 4.2% in liver recipients. The risk for miscarriage was 18% in kidney and 21% in liver recipients.

Pregnancy Outcomes in Transplant Recipients with Tacrolimus Exposure
New participants to the registry are predominantly on tacrolimus-based treatment regimens and these are reported by TPRI separately for kidney and liver transplant recipients. Female kidney and liver transplant recipients taking tacrolimus have reported successful pregnancies although, there continues to be a high incidence of prematurity < 37 weeks (42%-49%) and low birthweight <2500 grams (30%-42%) among the infants. The number of recipients exposed to MMF during the preconception and first trimester period is high in this group (27% and 29% for renal and liver recipients, respectively) and should be taken into consideration when reviewing the data for birth defects.

Cholestasis of pregnancy (COP) occurred in 7% of liver or liver-kidney recipient pregnancies in the TPRI, compared with approximately 1% of the general population.

7.2.4 Clinical Reviewer's independent search of the literature

In addition to the information provided by the applicant as part of the NDA submission, the clinical reviewer performed a search of published literature for clinical experience with tacrolimus administered during pregnancy and identified three relevant publications:

- Reyes et.al. Pregnancy after liver transplantation with tacrolimus immunosuppression: a single center's experience update at 13 years. Transplantation. 2003 Sep 15;76(5):827-32:

  Per the authors, this report reconfirms the safety of tacrolimus during pregnancy after liver transplantation and preterm delivery and low birth weight seem to be a persistent

problem in all solid-organ transplantation under any form of immunosuppression.

- Westbrook et.al. Outcomes of pregnancy following liver transplantation: The King's College Hospital experience. Liver Transpl. 2015;21(9):1153-9:

  The fetal outcomes demonstrated a live birth rate of 73%, no congenital abnormalities and only 1 child born at 24 weeks with delayed developmental milestones. However, the prevalence of low (19%) and very low birth weight (10%) was considerably higher than that of the general population. The authors concluded that the cause for the high incidence of prematurity and low birth weight in babies born to LT recipients remains unclear and is likely to be multifactorial, contributed by IS, the high incidence of pre-eclampsia/ eclampsia and iatrogenic delivery, ACR, and maternal comorbidity. In this study 81 patients were on tacrolimus, 34 on cyclosporine, 1 sirolimus, 1 azathioprine and steroids. Maternal complications encountered during pregnancy included hypertension (n=22), preeclampsia (n=16), eclampsia (n=3), gestational diabetes and cellular rejection.

- Webster et.al. Tacrolimus is an effective treatment for lupus nephritis in pregnancy. Lupus. 2014;23(11):1192-6:

  The authors stated that both tacrolimus and cyclosporine are associated with preterm delivery and low birth weight, complications that are also more common in women with lupus nephritis (LN). In the authors' view, in this series, tacrolimus was well tolerated, and the authors propose its use as either an adjuvant or alternative therapy to steroids in treating stable LN and disease flares during pregnancy, particularly due to the risk of harm to the fetus from conventional therapies.

Conclusions: Tacrolimus Related Fetal-Maternal Risk
Based on the applicant provided information in the NDA 210115 and the clinical reviewer Dr. Velidedeoglu's search of the published literature the following conclusions are reached:

- In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Based on the TPRI registry data, the same risks in transplant patients with tacrolimus exposure is 5-8% and 24-25% respectively and there does not seem to be a specific pattern in the reported congenital anomalies following tacrolimus exposure.

- Although the risk of previously mentioned adverse pregnancy outcomes seem to be increased in transplant patients with tacrolimus exposure, the exact role of tacrolimus in these adverse outcomes is not clear since transplant patients have other baseline conditions and confounders such as diabetes, hypertension, chronic end-stage organ failure prior to transplantation, concomitant drug exposures such as mycophenolic acid (MPA) products and corticosteroids.

- In the applicant's database search, there were 160 cases of tacrolimus exposure during pregnancies in nontransplant patients with no reported congenital anomalies. Based on the applicant's published literature search of pregnancy outcomes in non-transplant patients

with tacrolimus exposure, consisting of 40 patients, no pregnancy complications or congenital anomalies were reported. All deliveries took place after 37 weeks gestation, with adequate birth weight. These data from nontransplant patients suggest that many of the reported pregnancy complications and congenital anomalies after transplant may be a consequence of the underlying disease and other confounders, rather than from tacrolimus.

- The clinical reviewer's search of the published literature yields the similar conclusions to the applicant. In all three publications, there were no congenital anomalies reported both in transplant and nontransplant patients exposed to tacrolimus or cyclosporine during pregnancy except for one mother with Allagille Syndrome in the Reye et.al. publication. The possible contribution of tacrolimus to the observed adverse pregnancy outcomes cannot be ruled out with certainty.

- The general practice in transplantation seems to be to advise patients not to conceive during the first year following transplantation since tacrolimus exposure is generally higher than in subsequent. Based on the reported trough levels during pregnancy in the published literature, the tacrolimus exposure (target trough levels) may be intentionally lowered during pregnancies which concomitantly increases the risk of rejection.

- Among the major recognized fetomaternal risks potentially associated with tacrolimus exposure during pregnancy are gestational diabetes, perinatal jaundice, maternal hypertension, preeclampsia/eclampsia, premature birth, low birth weight, possible renal insufficiency in the newborn and electrolyte abnormalities in the newborn which are generally mitigated/treated successfully in clinical practice.
  The potential long term adverse outcomes on babies born to mothers with tacrolimus exposure during pregnancy may not be fully realized based on currently available data. These potential hypothetical risks include late occurring renal insufficiency during adulthood.

- The currently agreed upon PLLR language in the Prograf PI adequately conveys the potential fetomaternal risks associated with tacrolimus exposure during pregnancy.

9. Advisory Committee Meeting

This application did not raise any scientific issues that would warrant presentation and discussion before an Advisory Committee.

10. Pediatrics

This application received orphan designation, therefore PREA does not apply.

Since the application was submitted in response to a PMR, and included patient data and labeling, the application was presented before the Pediatric Review Committee (PeRC). An assessment was performed which agreed with the applicant's proposal to include labeling information in Section 6 Adverse Reactions, Section 8.4 summarizing the new pediatric information, summarizing the efficacy results from the controlled clinical study in liver transplant patients in Section 14.2.

The Division asked whether PK data on pediatric kidney and heart transplantation could be included in Section 12.3, because controlled studies in pediatric patients had not been performed. After discussion and questions, PeRC recommended that there was sufficient information to include labeling in pediatric patients for kidney and heart transplantation.

- The PeRC agreed with the division that the PREA PMR (2061-1, for NDA 204096, Astagraf XL) has been fulfilled and the product is fully assessed for the pediatric ages 1 to <5 years of age.

- In considering the appropriate formulation, PeRC, the Division and Applicant had determined that development of an age appropriate formulation for the immediate-release Prograf product would satisfy the PREA requirement for Astagraf XL because it was not possible to formulate an extended release product that could be taken by younger patients, and even the shorter-acting products may need to be given more than twice daily.

- Prograf was only approved for pediatric liver transplant patients and was not approved for use in pediatric kidney transplant patients because the adult indication was approved in 1997 (before PREA 2003) and the heart indication approved in 2006 had orphan designation and PREA did not apply.

- The Division stated that Orphan Drug Designation was granted for tacrolimus for oral suspension on October 4, 2016, for the prevention of rejection in heart, kidney, or liver transplant in pediatric patients.

- The PeRC asked the Division if there were sufficient data from published literature and from PK studies conducted with tacrolimus to appropriately label the product for use in pediatric liver, kidney, and heart transplantation, given the long history of use.

- Astellas did conduct clinical trials in support of Prograf Granules, (as summarized in the Clinical and Clinical Pharmacology sections of this review) – study FG-506-01-13 was a randomized, multi-center pediatric trial comparing the efficacy and safety of oral tacrolimus (granules) with cyclosporine in liver transplantation.

- The PeRC recommended labeling changes to include dosing for all three pediatric indications in Sec. 2.4 because efficacy can be established via extrapolation from adults for pediatric kidney and heart transplant patients and safety from the pediatric liver study.

- The PeRC also recommended including the pediatric PK data in Section 12.3 for all indications (kidney, heart and liver transplant patients).

PERC recommended the Division consult the Division of Pediatric and Maternal Health (DPMH) for labeling guidance, which was requested and the following is an excerpt from the final DPMH consult:

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population.

For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c) (9) (iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. Since the product will be indicated for use in pediatric patients, the information should be distributed throughout labeling as appropriate and summarized in 8.4 Pediatric Use.

The DPMH review addressed sections **8 Use in Specific Populations**, subsection **8.4 Pediatric Use**). The DPMH reviewer also recommended a brief summary under 8.4 cross-referencing to the other sections (Section 12.3 for PK data and Section 14.4 for clinical efficacy in pediatric liver transplant patients) and a brief discussion of the data used to support the safety, effectiveness and dosing in pediatric patients. DPMH recommendations are incorporated in these sections of the Prescribing Information (attached).

Conclusions / Comment: *The new information pertaining to the granule formulation including the starting dose and target trough levels for pediatric patients receiving liver transplants are included in the Dosage and Administration and other relevant sections of the package insert based on evidence of efficacy from a prospective, adequate and well controlled clinical trial. The trial demonstrated that in pediatric de novo liver transplant recipients on a Prograf® Granules (tacrolimus for oral suspension) based maintenance immunosuppressive treatment regimen had fewer acute rejections, fewer deaths and fewer graft loses and favorable safety when compared to a cyclosporine based maintenance immunosuppressive regimen.*

No randomized controlled trials have been performed and submitted in pediatric heart or kidney transplant recipients with the granule formulation; however, tacrolimus is commonly used off-label for these two indications in pediatric (heart or kidney) transplant patients. Use of PROGRAF capsules and PROGRAF for oral suspension in pediatric kidney and heart transplant patients is supported by adequate and well controlled studies in adult kidney and heart transplant patients with additional pharmacokinetic data from adult and pediatric patients and safety data in pediatric liver transplant patients as discussed in detail and agreed to during the PERC meeting. Therefore, the Dosage and Administration Section (2.4) provides recommended initial oral dosing for all three pediatric indications, for capsules or oral suspension.

11. Other Relevant Regulatory Issues

- **Office of Scientific Investigations (OSI) Audits** – because the one controlled trial in liver transplant pediatric patients with this formulation was conducted in 2000, source documents were not available, OSI recommended that site or applicant inspection were not warranted. In addition, since other formulations of tacrolimus have already been approved and marketed over 24 years, the main question was to characterize the

efficacy and safety of the new formulation and recommended dosage regimen. As summarized in the review section on Efficacy and Safety, no concerns were raised that would question the validity of the information presented. Case report forms for the individual patients in the controlled study were provided.

- **Office of Study Integrity and Surveillance (OSIS) Audits** – to assure the validity of the pharmacokinetic data (including trough concentrations which are used to guide treatment), the Office of Clinical Pharmacology requested OSIS to validate the assays used to measure tacrolimus concentrations. The inspection of Studies F506-CL-0403 (Modigraf PK) and PMR-EC-1206 (comparison of Astagraf XL and Prograf PK in pediatric transplant patients) and OCL117852 (not related to tacrolimus) were conducted at (b) (4) and the final inspection recommendation was No Action Indicated, and concluded that the data from these studies are reliable.

- **Dosage Form Determination** – the applicant's initial submission during the IND was Prograf (tacrolimus granules) Granules. However, it was determined that since the medication to be given to the patient would be in the form of an oral suspension, the established name for the dosage form should be – for oral suspension. There was concern that patients may sprinkle the granules on food. However, this concern will be addressed in the Patients Information and Instruction for Use provided to patients. Furthermore, after transplantation the parents or other care provider will be taught how to correctly use the product by the nursing coordinator or other trained professional, so they can correctly prepare the solution, before the transplant patients is discharged. When the clinical team agreed with the applicant request to seek the trade name PROGRAF Granules, it was noted that this name would cover both the drug and dosage form, thus it was recommended that the established name should include the active ingredient, and the established name should be (tacrolimus for oral suspension). The Trade Name PROGRAF® Granules has been approved by DMEPA.

12. Labeling

12.1 Prescribing Information

- The labeling has been updated to incorporate the information on the new PROGRAF Granules (tacrolimus for oral suspension) product in Sections 2.4, 6.1 (Table 8), 8.4, 12.3 and 14.2
- Pediatric efficacy in kidney and heart transplant has been extrapolated from adult studies and PK data and pediatric PK data, and is included in Section 2.4, 8.4 and 12.3.

12.2 Other Labeling

- The patient labeling include the Patient Information document providing information on the oral dosage forms (capsules, for oral suspension) and Instructions for Use in how to prepare the oral suspension using the packets containing the granules.

The labeling for these have been reviewed by the Division staff, and consulted to OPDP, DMEPA, and DMPP. The labeling has been finalized; the two documents are intended to be provided to the patient (or patient care giver) so they are familiar with information about Prograf, have a reference if questions arise, and can understand how to prepare the oral suspension, if questions arise.

- Carton and container labels have been reviewed and revised to reflect the updated Trade and established names for the 0.2 mg and 1 mg products.

- Proprietary Name Review – Astellas initially submitted the trade name Prograf® but during initial labeling discussion stated they wanted to add the qualifier "Granules" to the name. See Dosage Form Determination in Section 11 of this review. The Proprietary Name "PROGRAF® Granules" was granted 5/21/2018.

- Second DMEPA consult dated 05/22/2018 recommended that:
  - NDC numbers for the carton and container should be different – Astellas expressed concern that this would cause medication error and imply packets can be prescribed individually. DMEPA did not articulate the rationale for their suggestion. Astellas makes valid points that number should be the same to avoid inadvertent prescribing of packets and avoid medication errors. This issue was discussed with a licenced PharmD who agreed with this position.
  - The product is labeled to be reconstituted with water and not to sprinkle on food. However, DMEPA provides no justification or rationale for the new recommendation to not sprinkle granules on the tongue. Given that sprinkling on the tongue of this oral formulation would not raise concerns about stability or concerns about interaction with food, this is not an issue of concern. There is an IFU and extensive information about mixing with water, and if someone put the granules on the tongue and swallowed, and drank water, the product would have been administered orally. This is not the same as sprinkling on food, where there is potential concern about stability or interaction with food for oral suspension product. As already provided in approved labeling, tacrolimus should be administered consistently with food or without food, as the presence of food affects bioavailability.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

None

- Other Postmarketing Requirements and Commitments

None

50 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

----

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

OZLEM A BELEN
05/24/2018

RENATA ALBRECHT
05/24/2018